Can we prevent acute kidney injury?

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Objective: **To review the literature on prevention of acute kidney injury (AKI).**

Data Source: **MEDLINE- and PubMed-based review of literature published from 1965 to 2007.**

Conclusions: **AKI is very common among critically ill patients. Even mild forms of AKI have significant attributable mortality. Hence, it is imperative that every effort to prevent AKI be made in clinical practice. However, there are very few interventions that have been shown to consistently prevent AKI. Measures such as adequate hydration, maintenance of adequate circulating blood volume and mean arterial pressure, and avoidance of nephrotoxins are still the mainstay of prevention. Loop diuretics and "renal-dose" dopamine have been clearly shown not to prevent AKI and may, in fact, do harm. Among the remaining pharmacologic options, *N*-acetylcysteine has the strongest evidence in prevention of AKI. Fenoldopam and theophylline need further investigation before being used to prevent septic AKI and contrast nephropathy, respectively. The role of prophylactic dialysis in preventing contrast nephropathy needs to be investigated further. (Crit Care Med 2008; 36[Suppl.]:S166–S171)**

KEY WORDS: acute kidney injury; acute renal failure; dopamine; diuretics; prevention; *N*-acetylcysteine; theophylline; fenoldopam; radiocontrast nephropathy

Acute kidney injury comprises a family of syndromes that are characterized by an abrupt and sustained decrease in the glomerular filtration rate. In the intensive care unit (ICU), AKI is most often multifactorial, predominantly due to sepsis and other systemic inflammatory states. AKI is common among the critically ill and significantly adds to morbidity and mortality of these patients. Despite many advances in medical technology, the mortality and morbidity of AKI in the ICU continue to remain high and have not improved significantly during the past two decades. This article discusses the need to prevent AKI and the various options available and summarizes the evidence evaluating the various strategies. In this review, the term *acute kidney injury* (AKI) will be used to describe the entire spectrum of acute alterations in renal function, whereas *acute renal failure* (ARF) will be reserved for the more severe form of AKI (failure criteria by RIFLE classification) (1).

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WHY SHOULD WE PREVENT AKI?

As discussed in other reviews in this issue of *Critical Care Medicine*, AKI is common and associated with increased hospital mortality (2, 3). ARF is less common but associated with even higher mortality. In a recent large, multicenter, observational study of >29,000 critically ill patients, Uchino et al. (4) found that the most common contributing factor for ARF in the ICU was septic shock (47.5%), and the overall hospital mortality was 60.3%. The magnitude of the effect of AKI on outcomes can be recognized when one considers that the hospital mortality rate even in the control arm of the Acute Respiratory Distress Syndrome Network study evaluating low vs. traditional tidal volume strategies was only 40% (5). Importantly, in a departure from the "conventional wisdom" that patients die *with* and not *because* of ARF, there is now ample evidence that ARF is itself somehow associated with excess mortality, or in other words, ARF has "attributable mortality" (6, 7). Moreover, there is now clear evidence that even milder forms of AKI, not just ARF, and not just severe ARF requiring renal replacement therapy, are associated with excess mortality (2, 3, 8–10). Given the apparent effect of AKI on mortality, it is important to prevent or hasten the resolution of even the mildest forms of AKI. The goals of a preventive strategy for the syndrome of AKI are to preserve renal function, to prevent death, to prevent complications of AKI (volume overload, acid-base disturbances, and electrolyte abnormalities), and to prevent the need for chronic dialysis, with minimum adverse effects. Importantly, surrogate end points without direct, validated associations with clinical end points should not be taken as evidence of benefit. For example, an increase in urine output, transient change in creatinine clearance, or renal blood flow alone cannot be used as evidence of benefit because these end points have not been shown to be predictive of subsequent clinical effects. Even biochemical evidence of organ function (serum creatinine) should not be used unless it is sustained for several days after the intervention and seems to have reached steady state. In this review, the preventive strategies for AKI have been categorized into nonpharmacologic, pharmacologic, and dialytic strategies.

NONPHARMACOLOGIC STRATEGIES FOR AKI PREVENTION

Conservative methods to prevent AKI include limiting dehydration, hypotension, and exposure to nephrotoxins. Important strategies worth reviewing include fluids, maintenance of mean arterial pressure, aminoglycoside dosing, lipid preparations of amphotericin, and nonionic contrast agents.

Hydration and Volume Loading

Although there are no randomized controlled trials (RCTs) that have directly evaluated the role of fluids vs. placebo in the prevention of AKI, it has been recognized that intravascular volume depletion is an important risk factor for the development of AKI. Comparisons between outcomes in RCTs that have combined fluids (especially 0.45% sodium chloride infusion) with other active treatments and historical untreated controls, although not robust, suggest benefit from fluids (11). In certain settings, such as traumatic rhabdomyolysis, early and aggressive fluid resuscitation has clearly been shown to be beneficial (12). The route of fluid administration may make a difference in terms of outcome. In a small RCT, intravenous 0.9% saline hydration ($1\ mL{\cdot}kg^{-1}{\cdot}hr^{-1}$ for 24 hrs) begun 12 hrs before catheterization was compared with unrestricted oral fluid hydration in patients undergoing cardiac catheterization (13). In the intravenous saline group, 3.7% of patients developed contrast nephropathy, compared with 34.6% of patients in the unrestricted oral fluid group (relative risk [RR], 0.11; 95% confidence interval [CI], 0.015–0.79). Thus, intravenous hydration seems to be effective in prevention of at least some forms of AKI. Recent evidence also suggests that isotonic fluids are preferable to hypotonic fluid hydration in the prevention of AKI. An RCT of 1,620 patients comparing isotonic 0.9% saline with 0.45% saline with 5% dextrose found that infusion with 0.9% saline significantly reduced contrast nephropathy (0.7% with 0.9% saline vs. 2% with 0.45% in dextrose; $p = .04$) (14). More recently, a small, single-center RCT randomized patients to either infusion of isotonic sodium chloride ($n = 59$) or isotonic sodium bicarbonate ($n = 60$) before and after radiocontrast (iopamidol) administration (15). Prevalence of contrast nephropathy (defined as an increase of ≥25% in serum creatinine from baseline within 48 hrs) was 1.7% in the bicarbonate group, compared with 13.6% in the saline group ($p = .02$). This study had several limitations in that it was single-center study, did not use *N*-acetylcysteine, and that the incidence of contrast nephropathy in the control arm was very high compared with published incidence rates. However, this intervention is cheap and relatively risk free and hence can be considered in high-risk patients.

In summary, based on existing evidence, intravenous isotonic fluids are recommended in the prevention of AKI. However, the ideal composition of such a fluid (saline, Ringer's, bicarbonate based, or even colloid) and the optimal rate of infusion remain unclear and should be individualized to the patient's needs.

Maintaining Renal Perfusion Pressure

Specific recommendations to maintain perfusion are difficult to make given the absence of good clinical studies. However, several general principles are worth noting. First, no absolute number is considered adequate with regard to mean arterial pressure, and target mean arterial pressure should be individualized based on the patient's baseline physiology. Second, vasopressors should be used to improve perfusion pressure only after adequate volume repletion is accomplished, although in practice, vasopressors are often started as volume loading is underway and discontinued if no longer required once hypovolemia has been reversed (16). Third, contrary to common belief, there is no evidence from clinical studies or appropriately designed animal experiments to suggest that norepinephrine is associated with increased risk of AKI when used to treat arterial hypotension (17). Fourth, intra-abdominal hypertension is associated decreased renal perfusion and may result in AKI (18). Prompt recognition, monitoring, and early surgical treatment offer the best potential for recovery (18).

Nephrotoxin Exposure

Aminoglycosides, amphotericin, and radiocontrast are commonly encountered and studied nephrotoxins in the ICU.

Aminoglycoside Dosing. Aminoglycosides are common causes of drug-induced AKI. Sustained elevations in levels that occur from multiple daily doses seem to correlate with toxicity, whereas bacterial killing depends on peak concentrations. Moreover, aminoglycoside uptake by proximal tubular cells is saturable. Hence, when one large dose is given, more of the drug is excreted without undergoing tubular resorption and therefore without accumulating in the tubular cells and causing injury (19). Two meta-analyses and one systematic review have been performed comparing the efficacy and toxicity of multiple daily and once-daily aminoglycoside dosing schedules (20–22). All three studies have demonstrated that there were no differences in the efficacy of aminoglycosides when dosed once daily, but there was a trend toward lower nephrotoxicity in the once-daily dosing groups. These meta-analyses are methodologically limited in that the majority of trials focused on aminoglycosides other than gentamicin and tobramycin and included trials in which other nephrotoxic antimicrobials were used in combination with aminoglycosides.

Amphotericin B–Associated Nephrotoxicity. AKI associated with conventional amphotericin B occurs in 25–30% of patients, with progressive increase in the risk of AKI with increases in cumulative dose (23). The risk of renal dysfunction is relatively low at doses of $<0.5\ mg{\cdot}kg^{-1}{\cdot}day^{-1}$ and a cumulative dose of <600 mg. Although currently there is no definitive evidence that lipid formulations of amphotericin B result in less AKI, the use of lipid formulations of amphotericin B seems to cause less nephrotoxicity compared with standard formulations. In one small study of 55 patients with neutropenic fever, amphotericin B colloid dispersion was associated with equal therapeutic efficacy as conventional amphotericin B but reduced nephrotoxicity from 55% to 36% ($p < .001$) (24). Walsh et al. (25) compared liposomal amphotericin B with conventional amphotericin B as empirical antifungal therapy in 687 patients with persistent fever and neutropenia and showed that although liposomal amphotericin B was as effective as conventional amphotericin B for empirical antifungal therapy, it was associated with less nephrotoxicity (19% with amphotericin lipid complex vs. 34% in the conventional amphotericin B group; $p < .001$). On the basis of these data, lipid forms of amphotericin B should be used preferentially in patients with renal insufficiency or evidence of renal tubular dysfunction.

Radiocontrast Nephrotoxicity. The type and volume of contrast media administered influence the risk of contrast nephropathy in critically ill patients. A decreased incidence of contrast nephropathy seems to be associated with nonionic agents, which are either low osmolal (500–850 mOsm/kg) or iso-osmolal (approximately 290 mOsm/kg). One systematic review comparing "low-osmolality" contrast media with standard contrast media (26) showed that although low-osmolality contrast media did not influence the development of AKI or need for dialysis,

there was less nephrotoxicity with low-osmolality contrast media. Prospective trials comparing iodixanol (nonionic iso-osmolal media) with other agents have yielded conflicting results (27–29). A recent meta-analysis of 16 double-blind, controlled trials comparing iodixanol with low-osmolar contrast agents (n = 2,727) (30) showed that the incidence of contrast nephropathy (defined as an increase in Cr of ≥0.5 mg/dL within 3 days after contrast administration), was lower in the iodixanol group than in the low-osmolar contrast media group in all patients (1.4% vs. 3.5%, $p < .001$). There is also some recent indirect evidence to suggest that viscosity of contrast media might influence the incidence of nephrotoxicity (31, 32). For example, no significant differences exist in the reported rates of contrast nephropathy associated with iopamidol (low-osmolar contrast media with low viscosity) and iodixanol (iso-osmolar contrast media with higher viscosity). This can perhaps be explained by the increased viscosity of iodixanol relative to many of the low-osmolar agents. However, based on the existing evidence, the lowest volume necessary of nonionic, iso-osmolar, contrast medium should be used in conjunction with intravenous isotonic fluids in all high-risk patients.

PHARMACOLOGIC STRATEGIES FOR ARF PREVENTION

AKI in the ICU occurs in the setting of multiorgan failure, and numerous lines of evidence support inflammatory, oxidative stress and epithelial dysfunction as primary mechanisms of sepsis-induced AKI (33) rather than more traditional notions of ischemia (34). Moreover, pathologic specimens of patients with "acute tubular necrosis" show little or no changes that would be consistent with ischemia, further casting doubt on the notion of impaired renal blood flow in sepsis. Therefore, not surprisingly, pharmacologic strategies predicated on the notion of increasing renal blood flow or decreasing renal oxygen consumption have been generally unsuccessful. Although many agents have been shown to improve renal blood flow, renal plasma flow, glomerular filtration rate, or urine output, clinical benefit has not been consistently shown with any of these agents.

Loop Diuretics

Oliguria accompanying AKI is, in part, due to tubular obstruction caused by debris, including denuded epithelium, and this obstruction potentially leads to the back leak of glomerular filtrate into the renal interstitium, further perpetuating renal injury. Moreover, nonoliguric AKI has often been shown to have a better prognosis than oliguric AKI. Hence maintaining a greater urine flow to "flush" out the tubules with loop diuretics has been advocated to prevent AKI. Two meta-analyses have pooled studies evaluating the role of loop diuretics in the prevention of AKI. The first systematic review compared fluids alone with diuretics in people at risk for AKI from various causes and found no benefit from diuretics with regard to its incidence, need for dialysis, or mortality (35). In the second recent meta-analysis (RCTs, n = 849 patients), no difference among patients treated with loop diuretics was found in hospital mortality, need for renal replacement therapy, or number of dialysis sessions needed (36). However, an increased risk of temporary deafness and tinnitus in patients treated with high doses of furosemide (RR, 3.97; 95% CI, 1.00–15.78) was noted.

Based on these data, it is possible to conclude that there is no evidence to support the use of loop diuretics in the prevention of AKI from any cause. It is also clear that loop diuretics do not decrease the need for renal replacement therapy or decrease the number of dialysis sessions. However, whether a trial of loop diuretic in patients with oliguric AKI before initiation of dialysis is safe and effective is under immense debate. However, two observational studies have provided similar results (37, 38). In the first observational study, with adjustments for relevant covariates and propensity scores, loop diuretic use in patients with AKI was associated with significantly increased risk of death or nonrecovery of renal function (odds ratio, 1.77; 95% CI 1.14–2.76) (37). In a subsequent larger, multinational, multicenter study, three multivariate models were performed to assess the relationship between loop diuretics and mortality (38). Although this study failed to find a statistically significant association between diuretic use and increased mortality, the odds ratio for death was still on the side of harm (1.2 in all three models). In summary, if a loop diuretic trial is considered before dialysis in patients with oliguric AKI, such a trial should be terminated quickly if not effective in causing diuresis, to avoid delayed dialysis and ototoxicity. Thus, although diuretics may be useful and even necessary in the management of volume overload, they have no role in the prevention of AKI and the treatment of oliguria.

Dopamine Agonists

Dopamine increases renal blood flow by direct splanchnic vasodilation, increasing the cardiac output and the perfusion pressure, and hence has been evaluated extensively in the prevention and treatment of AKI. Multiple small studies have provided conflicting results and have evaluated surrogate end points with no clinical significance. Three systematic reviews and one large RCT have evaluated the role of dopamine in preventing deterioration of renal function in the ICU (39–42) and have unequivocally concluded that dopamine did not prevent onset of ARF, need for dialysis, or mortality. Thus, based on current evidence, there is absolutely no role for low-dose dopamine in the prevention of AKI from any cause.

Fenoldopam, a selective dopamine-1–receptor agonist, similar to dopamine, has been shown to increase renal blood flow and glomerular filtration rate (43). The largest RCT has evaluated the role of fenoldopam in the prevention of contrast nephropathy. In this study, 315 patients with creatinine clearance of <60 mL/min were randomized to fenoldopam mesylate or placebo (44). The incidence of contrast nephropathy (25% increase in serum creatinine within 96 hrs postprocedure) was similar in both groups (33.6% in the fenoldopam group vs. 30.1% in the placebo group; RR, 1.11; 95% CI, 0.79–1.57; $p = .61$). However, a recent single-center study randomized ICU patients to a continuous infusion of either fenoldopam (n = 150) at 0.09 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or placebo (n = 150) (45). The incidence of ARF was significantly lower in the fenoldopam group compared with the control group (29 vs. 51 patients; $p = .006$). Finally, a recent meta-analysis included RCTs evaluating fenoldopam in ICU patients or those undergoing major surgery but excluded studies of contrast nephropathy (16 RCTs and 1,290 patients) (46). This analysis showed that fenoldopam significantly reduced the risk for AKI (odds ratio, 0.43; 95% CI, 0.32–0.59; $p < .001$), need for renal replacement therapy (odds ratio, 0.54; 95% CI, 0.34–0.84; $p = .007$), and in-hospital death (odds ratio, 0.64; 95% CI, 0.45–0.91; $p = .01$). This study was limited in that it excluded studies involving the prevention of contrast nephropathy from

analysis, included studies with varied doses, and contained only five small placebo-controlled studies. Hence, based on existing evidence, it is safe to conclude that fenoldopam has no role in the prevention of contrast nephropathy. However, further studies are needed to evaluate its efficacy in preventing AKI from other causes in the ICU. It should be remembered that hypotension is a very common side effect of fenoldopam and, without close monitoring and treatment, can lead to harm in ICU patients with AKI.

Natriuretic Peptides

Many RCTs have evaluated atrial natriuretic peptides in the prevention of AKI and have failed to show any benefit (47–49). In the largest RCT, prospectively defined subgroup analysis suggested that oliguric patients (<400 mL of urine per day) had improved dialysis-free survival ($p = .008$) in comparison with the placebo group, whereas nonoliguric patients had worsened dialysis-free survival with anaritide than control groups ($p = .03$) (47). However, in a subsequent RCT in oliguric patients, anaritide did not improve dialysis-free survival (49). Interestingly, a recent, small, single-center RCT studied 61 postcardiac surgery patients using a continuous infusion of low-dose human recombinant natriuretic peptide (50 $ng \cdot kg^{-1} \cdot min^{-1}$) (50). This trial, unlike the larger studies in past, showed a decreased use of dialysis (hazard ratio, 0.28; 95% CI, 0.1–0.73; $p = .009$) and improved dialysis-free survival in treated patients compared with placebo. This positive study differed from the previous negative studies in that a very low dose of atrial natriuretic peptide was used for a long period of time and that special efforts to identify hypotension and treat it were undertaken by the investigators. In general, anaritide should not be used to prevent AKI in ICU patients. Furthermore, larger RCTs are necessary in the cardiac surgical population with low-dose human recombinant natriuretic peptide before its routine clinical use in this population.

Calcium Channel Antagonists

It is now known that acute elevation in intracellular calcium precedes any evidence of renal tubular membrane damage in certain forms of AKI (51). Moreover, calcium antagonists have been shown to reverse the afferent arteriolar vasoconstriction induced by a variety of stimuli, but the efferent arteriole seems to be highly refractory to the vasodilatory effects of calcium antagonists (52). In addition, calcium antagonists have a natriuretic effect independent of their effects on the renal microvascular hemodynamics (53). For all the above reasons, calcium channel antagonists have been evaluated in the prevention of AKI, especially transplant-associated nephropathy. Multiple small studies have provided conflicting results. However, the largest multicenter, prospective RCT, which evaluated the effect of isradipine on renal function, incidence and severity of delayed graft function, and acute rejection after kidney transplantation, did not show any benefit with this class of drugs (54). In this study, 210 patients who received a cadaveric or non-HLA-identical living donor kidney were randomized to receive either isradipine or placebo. Although median serum creatinine levels at 3 months and 12 months were significantly better in the isradipine group, there was no statistical difference in the incidence and severity of delayed graft function or biopsy-proven acute rejection between the groups. Subsequently a systematic review evaluated the benefits and harms of using calcium channel blockers in the peritransplant period in patients at risk of acute tubular necrosis after cadaveric kidney transplantation (55). Only RCTs comparing calcium channel blockers given in the peritransplant period with controls were included. This review included nine RCTs and concluded that treatment with calcium channel blockers in the peritransplant period was associated with a significant decrease in the incidence of posttransplant acute tubular necrosis (RR, 0.57; 95% CI, 0.40–0.82) and delayed graft function (RR, 0.44; 95% CI, 0.28–0.69). However, there was no difference between control and treatment groups in graft loss, mortality, or requirement for hemodialysis. However, the trials included were very heterogenous and used different classes, doses, and routes of calcium channel blockers. Hence, based on current evidence, calcium channel blockers cannot be routinely recommended in patients to prevent AKI.

Adenosine Antagonists (Theophylline)

Several small clinical studies have been done to evaluate the role of theophylline, an adenosine antagonist, in the prevention of contrast nephropathy and have shown discordant results (56–58). However, a recent meta-analysis showed that patients who received theophylline had a smaller increase in serum creatinine compared with those who received placebo ($p = .004$) (59). However, this meta-analysis was limited in that it included studies that did not control for hydration status and used changes in creatinine as the end point rather than predefined criteria for AKI. Accordingly, it remains unclear if theophylline might be useful in preventing contrast nephropathy. However, larger multicenter RCTs examining valid clinical outcomes (e.g., AKI, dialysis requirement, mortality) will be necessary to adequately address this issue before routine use of theophylline to prevent contrast nephropathy can be recommended.

N-Acetylcysteine

The use of *N*-acetylcysteine (NAC) in several small studies has been shown to decrease the incidence of contrast nephropathy, defined as a 25% increase in serum creatinine after radiocontrast administration (60–62). Subsequently, several meta-analyses have pooled the existing data to evaluate the role of NAC in the prevention of contrast nephropathy. In the largest meta-analysis (63), the pooled random effect RR was 0.65 (95% CI, 0.43–1.00; $p = .049$), indicating that NAC significantly reduced the incidence of contrast nephropathy. However, there was evidence of significant heterogeneity in NAC effect across studies.

Moreover, all these studies have to be interpreted in the light that NAC has been shown to decrease serum creatinine without improving glomerular filtration rate (64), possibly by activating creatinine kinase activity and possibly by increasing tubular secretion. Hence, as of now, the implications of dose-dependent reduction in serum creatinine after contrast administration with the use of NAC remain unclear and need to be further explored. However, considering its safety, low cost, and possible benefit, NAC can be used in high-risk patients to prevent contrast nephropathy. It is important to realize that NAC should not be used as a replacement for adequate intravenous hydration with an isotonic fluid.

DIALYTIC STRATEGIES FOR AKI PREVENTION

Although contrast media can be removed by dialysis (65), insufficient evi-

Table 1. Prevention of acute kidney injury (AKI)

Strategies recommended to prevent AKI
I. Intravenous isotonic hydration
II. Maintenance of "adequate" mean arterial pressure
III. Minimizing nephrotoxin exposure
a. Once daily dosing of aminoglycosides
b. Use of lipid formulations of amphotericin B
c. Use of low-volume nonionic iso-osmolar contrast media
Strategies that may help prevent contrast nephropathy
I. *N*-acetylcysteine
II. Hydration with sodium bicarbonate
Strategies that need further evaluation
I. Low-dose human recombinant atrial natriuretic peptide (in cardiac surgical patients)
II. Low-dose fenoldopam (septic patients)
III. Theophylline (patients receiving contrast media)
IV. Prophylactic hemofiltration (patients receiving contrast media)
Strategies that have no role in the prevention of AKI
I. Loop diuretics
II. Low-dose dopamine
III. Atrial natriuretic peptide
IV. Fenoldopam (in prevention of contrast nephropathy)

dence exists for the routine use of prophylactic dialysis to prevent contrast nephropathy. One small, single-center RCT has evaluated the role of low-dose hemofiltration with hydration alone in the prevention of contrast nephropathy and found that hemofiltration decreased the incidence of contrast nephropathy, in-hospital mortality, and 1-yr cumulative mortality (66). However, this study had several important limitations, including the lack of a standardized hydration regimen and lack of iso-osmolar contrast media or NAC. Finally, the study compared ICU care plus hemofiltration with care on the medical ward. Thus, based on existing evidence, prophylactic hemofiltration cannot be routinely recommended to prevent contrast nephropathy.

CONCLUSIONS

AKI occurs commonly in critically ill patients. Even modest derangements in renal function significantly worsen mortality and add to the morbidity. Thus, considerable effort has been expended to develop techniques to prevent AKI or to facilitate its resolution. Unfortunately, preventing the development of AKI in at-risk populations is an attractive but difficult goal. Well-powered studies have failed to demonstrate that drugs, such as low-dose dopamine, atrial natriuretic peptide, and diuretics, can prevent onset or deterioration of renal function in the critically ill, and there is the potential to cause harm. The best available options are still disappointingly empirical. Strategies such as avoidance of hypotension and dehydration and minimizing exposure to nephrotoxins, though intuitive, lack strong evidence (Table 1). Once-daily dosing of aminoglycosides and lipid formulations of amphotericin B seem to minimize AKI. Similarly, using the lowest volume of nonionic iso-osmolar contrast media is recommended to minimize the prevalence of contrast nephropathy. Loop diuretics have no role in the prevention of AKI. A short trial of diuretic in an oliguric patient before dialysis may be reasonable, but there is no evidence to suggest that the need for dialysis will be reduced with such a strategy. Recently, pooled data from small studies suggest that NAC can reduce the incidence of AKI secondary to radiocontrast agents. Given its low cost and excellent side-effect profile, it would seem prudent to provide NAC along with intravenous fluids to all patients with underlying renal insufficiency and to those with diabetes or underlying cardiovascular or hepatic disease who are receiving intravenous radiocontrast. The roles of fenoldopam in preventing sepsis-induced AKI and theophylline in preventing contrast nephropathy need to be explored more in larger clinical trials. There is no definitive evidence to recommend prophylactic hemofiltration to prevent contrast nephropathy.

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